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Preparation of chiral thioureas, ureas and guanidines from (*S*)-2-(*N*,*N*-dialkylaminomethyl)pyrrolidines

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Abstract—The reaction of commercially available heterocumulenes (isothiocyanates, isocyanatobenzene, *N*,*N*′-isopropylcarbodiimide) with lithiated chiral diamines **4** provided a novel class of chiral thioureas **8**, ureas **9** and guanidines **10**, which were isolated in good to excellent yields (60–96%). The molecular structures of compounds **8**–**10**, derived from (*S*)-2-(*N*,*N*-dialkylaminomethyl)-pyrrolidines **1**–**3**, were determined.

1. Introduction

Derivatives of chiral thiourea and urea are used as ligands for the asymmetric reduction of prochiral ketones to afford chiral alcohols.[1] They are also applied in the asymmetric hydrogenation of enamides[2] and as catalysts for the Strecker reaction.[3] Another application is the enantioselective amino acid recognition by using acyclic thiourea receptors.[4] Furthermore, chiral thioureas and ureas are nonnucleoside inhibitors (NNI) of the human immunodeficiency virus (HIV) reverse transcriptase.[5]

Guanidines and guanidinium salts have attracted increasing research interest during recent years. The importance of chiral guanidinium salts is particularly reflected in many biologically active compounds, which exhibit molecular recognition towards oxy-anions such as carboxylates or phosphates.[6] Due to their strongly basic character, guanidines can also be considered as superbases.[7] It has been reported that chiral guanidines can be employed as chiral auxiliaries in asymmetric syntheses, such as in Michael reactions, nucleophilic epoxidations or nitroaldol reactions.[8,9]

Herein, we describe the preparation of chiral thioureas, ureas and guanidines by a convenient method using chiral amines and selected heterocumulenes, for example, isothiocyanatobenzene **5a**, isocyanatobenzene **6** and *N*,*N*′-diisopropylcarbodiimide **7**. The reaction of chiral amines with isocyanates[10] or carbodiimides[11] has been extensively investigated. Stimulated by the formation of chiral carbamates starting from (*S*)-2-(*N*,*N*-dialkylaminomethyl)pyrrolidines and carbon dioxide,[12] we focused our investigations on extending this convenient simple synthesis and on obtaining novel chiral thioureas, ureas and guanidines. Most importantly, this synthesis represents a simple route to chiral derivatives of these diamines.

Our ongoing research program[13] is devoted to the investigations of heterocumulene reactions with chiral diamines.[12] These lithiated chiral diamine derivatives **4** have been used previously for enantioselective deprotonations of *meso*-epoxides to yield allylic alcohols in high enantiomeric excess.[14] For example, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide deprotonates cyclohexene oxide in THF to afford (*S*)-cyclohex-2-en-1-ol with 80% ee.[15]

To our knowledge, no attempts to synthesize chiral thioureas, ureas and guanidines starting from (*S*)-2-(*N*,*N*-dialkyl-aminomethyl)pyrrolidines have been published to date.

2. Results and discussion

Preparation and structural assignment of chiral thioureas **8a**–**i**, ureas **9a**–**c** and guanidines **10a**–**c** from (*S*)-2-(*N*,*N*-dialkyl-aminomethyl)pyrrolidines:

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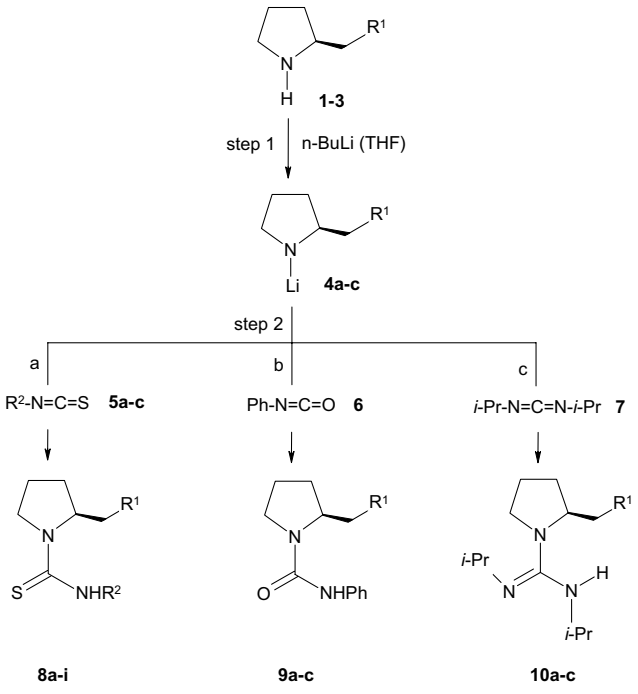
The starting materials, enantiomerically pure diamines **1**–**3**, are readily prepared from commercially available compounds in a three-step reaction following method from literature.[16]

We first checked the reaction of the chiral diamines **1**–**3** with the cumulenes **5a** and **7**. The results were disappointing: In a typical run, after 3 h of heating under reflux and purification, compounds **8a** and **10a** were obtained in very moderate yields (**8a**: 55%, **10a**: 32%). Therefore, we decided to synthesize the lithiated amides **4a**–**c** first. The latter have been shown to be excellent reagents to react with carbon dioxide to give the corresponding chiral lithium carbamates in good to excellent yields under very mild reaction conditions.[12]

Thus, in all cases the proline-derived amines were quantitatively converted with 1.6 M *n*-butyllithium solution (Scheme 1, step 1) to the corresponding lithium amides **4a**–**c**, which were in situ reacted with the cumulenes. The over-all reactions to **8**, **9** and **10** proceed without noticeable racemization as proven by NMR experiments under application of a chiral shift reagent (vide infra, Experimental Part).



Scheme 1. Preparation of **8a**–**i**; **9a**–**c** and **10a**–**c**: R^1, R^2: see Table 1.

2.1. Thioureas 8a–i (Scheme 1 and Table 1)

Treatment of **4a**–**c** with isothiocyanates **5**, without purification of intermediate lithium salts of the chiral thioureas **8a**–**i** afforded the expected chiral thioureas **8a**–**i** after hydrolysis in good to excellent yields (Scheme 1, step 2a). Commercially available isothiocyanatobenzene **5a**, 1-isothiocyanato-4-methoxybenzene **5b** and 1-isothiocyanato-2-methyl-propane **5c** were used as heterocumulene substrates (Table 1).

Table 1. Results for the preparation of **8a**–**i**

Thioureas	R^1	R^2	Yield[a] (%)	$[\alpha]_D^{rt}$
8a	1-Pyrrolidinyl	Ph	94.4	−138.7
8b	4-Morpholinyl	Ph	96.0	−200.0
8c	1-Piperidinyl	Ph	97.2	−141.3
8d	1-Pyrrolidinyl	*p*-MeO-Ph	94.3	−138.7
8e	4-Morpholinyl	*p*-MeO-Ph	67.9	−158.8
8f	1-Piperidinyl	*p*-MeO-Ph	84.1	−136.3
8g	1-Pyrrolidinyl	Isopropyl	67.2	−131.1
8h	4-Morpholinyl	Isopropyl	67.4	−91.0
8i	1-Piperidinyl	Isopropyl	67.2	−110.0

[a] Isolated yields.

The molecular structures of compounds **8a**–**i** were established from their NMR (^{1}H, ^{13}C, DEPT 135, HMQC, HMBC) spectroscopic data. The reaction of the NCS group and the ring nitrogen was elucidated by ^{13}C NMR spectroscopy. As expected, the C=S carbon atom was observed in the ^{13}C spectra at 179–183 ppm for all compounds **8a**–**i**. Generally, ^{1}H NMR spectra showed multiplet signals due to the existence of one stereogenic centre. The NH protons were detected as a broad singlet in the range of 8–12 ppm. Interestingly, the methyl protons of **8g**–**i** in the ^{1}H NMR spectra emerged not as the expected doublet but as one triplet. For example, the ^{13}C NMR spectra of **8g** showed two nonequivalent carbon signals at δ values of 22.1 and 23.2. The respective protons appeared as a triplet in the ^{1}H NMR spectrum at the value of δ 1.23. The isopropyl CH signal was observed at $\delta = 4.56$ as a septet ($J = 6.6$ Hz), indicating that the CH proton is coupled with the methyl protons. This resulted from the stereogenic centre and a likely strong intramolecular hydrogen bond between isopropyl nitrogen and the second pyrrolidine ring nitrogen. By a high level DFT calculation (Gaussian 98[17] B3LYP[18] level with the 6–31+G(d)[19] basis set) the bridging interaction in **8a** was determined. The strength of the hydrogen bond in **8a** was calculated to be 21.5 kcal mol^{-1} by using the NBO analysis.[20,21] Additionally, a DFT search for variants of **8a** without intramolecular hydrogen bond was performed. Compound **8a′** appears to be the most stable structure while a manifold of similar starting geometries collapsed into **8a**. It was found that this nonhydrogen bond stabilized conformer **8a′** is 12.4 kcal mol^{-1} less stable than **8a** (Fig. 1, ZPE corrected). This difference between **8a** and **8a′** again indicates the remarkable energetic gain caused by this hydrogen bond. These findings indicate that chiral thioureas **8a**–**i** exhibit the respective H-bond stabilized structure in solution.

In order to obtain additional insight in the proposed structure for the chiral thioureas **8a**–**i**, an X-ray structure analysis of **8a** was performed (Fig. 1).[22] The crystal structure shows the correct expected (*S*)-configuration, and an intramolecular hydrogen bond interaction between N(1) and N(3) as indicated by the dashed line. The agreement between the experimental and the calculated structure of **5a** is excellent (cf. Fig. 1).

2.2. Ureas 9a–c (Scheme 1 and Table 2)

Trisubstituted chiral ureas **9a**–**c** were prepared analogously from the lithiated intermediates **9a**–**c** by reaction

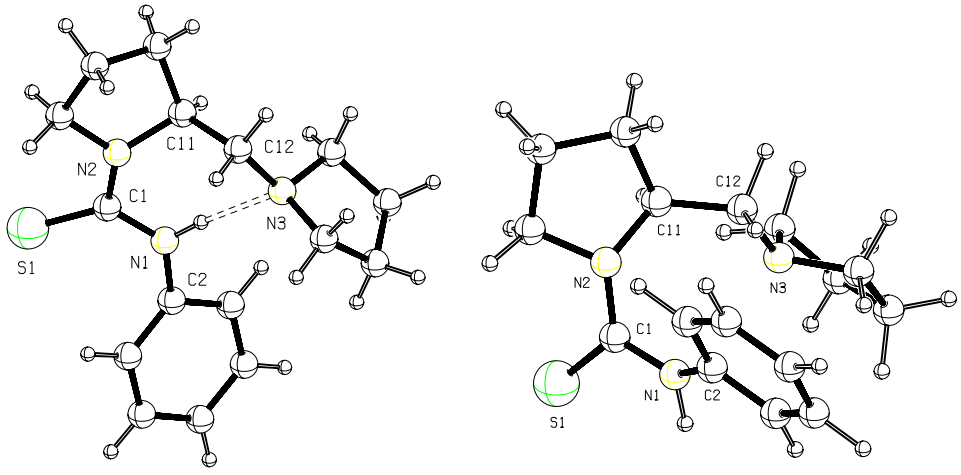


Figure 1. Crystal structure of **8a**, a representative of the novel chiral thioureas. For further crystal structures cf. supporting information. Selected bond lengths (Å) and bond angles (deg): S(1)–C(1) 1.687(3), N(1)–C(2) 1.419(4), N(3)–C(12) 1.452(4), N(1)–C(1) 1.353(4), N(2)–C(1) 1.353(4), N(2)–C(1)–S(1) 121.0(3), N(3)–C(12)–C(11) 112.5(3), N(2)–C(1)–N(1) 114.7(3), N(2)–C(11)–C(12) 114.4(3); Calculated structure of **8a**: bond length (Å) and bond angles (deg): S(1)–C(1) 1.690, N(1)–C(2) 1.424, N(3)–C(12) 1.464, N(1)–C(1) 1.368, N(2)–C(1) 1.375, N(2)–C(1)–S(1) 121.4, N(3)–C(12)–C(11) 112.8, N(2)–C(1)–N(1) 114.3, N(2)–C(11)–C(12) 113.5. Calculated structure of the conformer **8a′**: selected bond lengths (Å): S(1)–C(1) 1.679, N(1)–C(2) 1.412, N(1)–C(1) 1.389, N(2)–C(1) 1.389.

with isocyanatobenzene **6**. Stirring of a mixture of **4a**–**c** and **6** in THF at 25 °C gave the lithium salts of **9a**–**c**. After hydrolysis, **9a**–**c** were obtained as white precipitates in good to excellent yields (Scheme 1, step 2b, Table 2).

Table 2. Ureas **9a**–**c** prepared

Ureas	R^1	Yield[a] (%)	$[\alpha]_D^{rt}$
9a	1-Pyrrolidinyl	86.9	−53.3
9b	4-Morpholinyl	71.1	−62.1
9c	1-Piperidinyl	96.1	−60.8

[a] Isolated yields.

Some NMR details of ureas **9a**–**c**: As expected, the C=O carbon atom (150–155 ppm) appeared in the ^{13}C spectra at a lower field than the C=S carbon atom (179–183 ppm) for compounds **8a**–**c**. The ^1H NMR ($CDCl_3$) of **8a**–**c** revealed significant shifts of the NH proton now showing a broad singlet in the range of 9–11 ppm, corresponding to the NH protons of the thioureas **8a**–**c**. The aliphatic protons were also diastereotopic, appearing as complex multiplets. The aromatic protons of **9a**–**c** appeared as multiplets in the range from 6.8 to 7.5 ppm.

2.3. Guanidines 10a–c (Scheme 1, Table 3)

Lithiation of **1** with *n*-butyllithium (1.6 M in *n*-hexane) followed by treatment with **7** without purification of the intermediate lithium salt of **10a** afforded after hydrolysis the desired guanidine **10a** in moderate to good yield. Similarly, the analogues educts **2** and **3** led to the corresponding guanidines **10b** and **10c** (Scheme 1, step 2c). This simple method provides a direct route to enantiomerically pure guanidines **10a**–**c** from numerous available chiral diamines[23] and carbodiimides.[24] The results are summarized in Table 3. Although $CDCl_3$ was used as solvent for all other compounds, the NMR measurements of **10a**–**c** were recorded in THF due to the strong basic character of these guanidines. To elucidate the structures of **10a**–**c**, 2D NMR experiments (HMQC, HMBC, COSY, NOESY, TOCSY) were carried out at room temperature and at −40 °C in addition to ^1H, ^{13}C and DEPT 135. The ^{13}C spectra exhibited the expected number of signals and the guanidine carbon atom appeared in the range of 152–153 ppm. In the ^1H NMR spectrum, the NH guanidine protons were observed as doublets in the region of δ 3.9–4.1 ppm. Considering example **10a**, the isopropyl methine carbon atoms emerged as separate signals in ^{13}C NMR at the value of δ 46.6 and 47.7 ppm. The appropriate protons appeared as two overlayered septets in the range of 3.40 ppm. The corresponding methyl protons can be assigned to three doublets at the value of δ 1.12 (3H), 1.03 (6H) and 0.94 (3H) for the NH isopropyl group and the imine isopropyl group. To assign the methyl signals to the corresponding CH groups a selective ^1H–^1H-TOCSY was employed. The TOCSY spectrum revealed correlations between isopropyl NH at δ 4.03, the methine proton at δ 3.42 and the doublets at δ 1.12 and δ 1.03. Thus, the imine isopropyl group assigned to the CH proton at δ 3.39 and the doublets at δ 0.94 and 1.03. The splitting of the ^1H and ^{13}C signals is presumably due to a strong hydrogen bond between the isopropyl NH group and the second pyrrolidine ring nitrogen. The strength of the

Table 3. Preparation of chiral guanidines **10a**–**c**

Guanidines	R^1	Yield[a] (%)	$[\alpha]_D^{rt}$
10a	1-Pyrrolidinyl	71.9	−3.0
10b	4-Morpholinyl	75.9	−11.1
10c	1-Piperidinyl	78.3	−16.6

[a] Isolated yields.

hydrogen bond in the guanidine **7c** was calculated to be 9.2 kcal mol^{-1}.[20,21] Thus, the molecule is restricted in its rotational movement between the isopropyl nitrogen and the nitrogen of the second pyrrolidine ring owing to this H-bond and hence, the chemical environments for the methyl groups and methine groups are different. The influence of the stereogenic centre should be kept clearly in mind.

To confirm the correct absolute configuration of the chiral guanidines **10a**–**c**, a hydrochloride of **10a** was crystallized and the structure was established by X-ray crystallography.[25] The X-ray analysis of **10a·(HCl)$_2$** provided the expected (*S*)-configuration of the C2-carbon (Fig. 2).

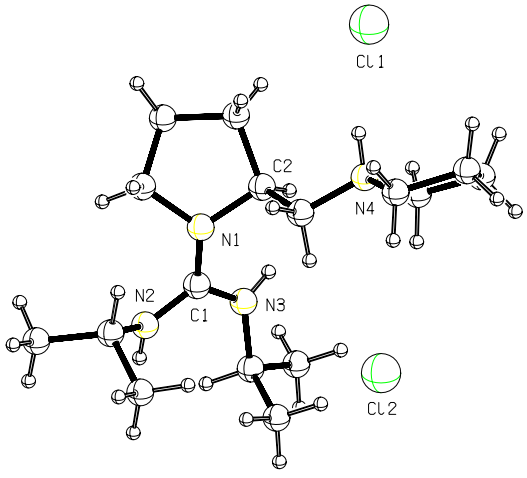


Figure 2. Crystal structure of **10a·(HCl)$_2$**. Selected bond lengths (Å) and bond angles (deg): N(1)–C(1) 1.349(3), N(2)–C(1) 1.336(3), N(3)–C(1) 1.335(3), N(2)–Cl(2) 3.083, N(4)–Cl(1) 3,326, C(1)–N(1)–C(2) 123.4(2), N(4)–C(1)–N(3) 120.3(2), N(3)–C(1)–N(1) 119.4(2), N(4)–C(1)–N(1) 120.2(2).

3. Conclusion

In summary, our results represent a convenient way to prepare quite different chiral thioureas **8a**–**i**, ureas **9a**–**c** and guanidines **10a**–**c** by an effective synthesis of optical active diamines with isothiocyanates **5a**–**c**, isocyanatobenzene **6** and *N*,*N*′-diisopropylcarbodiimide **7**. The reaction conditions are mild, the intermediate chiral lithium amides can be reacted with the cumulenes in situ.

In our further research, the successful preparation of **8a**–**i** and **9a**–**c** provided a new type of chiral ligands for using in asymmetric syntheses.[4] The chiral guanidine synthesis was applied to just one alkylcarbodiimide. Nevertheless, our results indicate that this method should be applicable for the preparation of a wide variety of chiral guanidines such as **10a**–**c** from appropriate chiral diamines. We are currently seeking to extend the guanidine chemistry to investigate its application in asymmetric syntheses, for example, in Michael additions as chiral bases.

4. Experimental

4.1. General methods

Melting points are uncorrected. NMR spectra were recorded at 250 or 400 MHz and 62.5 or 100 MHz, for proton and carbon, respectively. For ^{1}H and ^{13}C, $CDCl_3$ (H $\delta = 7.24$, C $\delta = 77.0$) and THF-d_8 (H $\delta = 3.58$, C $\delta = 67.4$) were used as solvents, and TMS was used as internal standard. Optical rotations are reported as $[\alpha]_D^{rt}$ (*c* in g per 100 mL, solvent). All compounds were fully characterized and given microanalytical data (±0.4%) or HRMS. Isocyanatobenzene, isothiocyanatobenzene, 1-isocyanato-4-methoxybenzene, 1-isothiocyanato-2-methylpropane, *N*,*N*′-diisopropylcarbodiimide and *n*-butyllithium (1.6 M) in *n*-hexane were commercially available and used without further purification. Chiral diamines **1**–**3** are described in the literature.[16] Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone. Characterization data of **8b**–**i**, **9b**, **9c**, **10b** and **10c**, crystal structure determination and crystal data for **8a**, **8d**, **8h**, **9c** and **10a·(HCl)$_2$** are available.

^{1}H NMR investigations of **8a**, **9a** and **10a** were carried out in the presence of the shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in order to assess the enantiomeric purity.[26] **8a** (0.02g, 0.070 mmol) was dissolved in $CDCl_3$ (**10a** in THF-d_8) and 0.01 g (0.035 mmol) shift reagent was added (0.07 mmol was applied for **10a**). Additionally, the reliability of the shift reagent was tested with the racemates of **8a**, **9a** and **10a**. The 1:1 mixture of the diastereomeric complexes formed with that shift reagent show in all cases two well-separated ^{1}H NMR multiplets of the bridging CH_2-pyrrolidine group at the stereogenic C(2) centre of the pyrrolidine ring, which can be assigned to the individual diastereomers. The reference frequency shifts differ by 13.2 Hz (**8a**), 13.3 Hz (**9a**) and 1.9 Hz (**10a**).

In the case of the enantiomerically pure starting compounds, no racemization has been observed within the NMR accuracy. Thus, the enantiomeric purity of isolated compounds **8**, **9** and **10** is higher than 95%.

4.2. General procedure for the preparation of chiral thioureas 8a–i

4.2.1. *N*-Phenyl-(*S*)-2-(pyrrolidin-1ylmethyl)pyrrolidine-1-carbothioamide 8a. A stirred solution of **1** (1 g, 6.5 mmol) in dry THF (20 mL) was cooled to −30 °C and *n*-butyllithium (4.1 mL, 6.5 mmol) was slowly added in an inert atmosphere. The yellow mixture was warmed at room temperature and stirred for 1 h. Compound **5a** (0.88 g, 6.5 mmol) was slowly dropped to the obtained lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolin-1-ide **4a** solution, and the mixture was stirred for 2 h at room temperature. The solution was evaporated (10 mL) under vacuum and the residue was added in ice water (100 mL). The resulting yellow precipitate was filtered off and washed with *n*-heptane or ether. The rest of the solvent was evaporated under reduced pressure to afford **8a** as a white solid in analytical purity, mp 137 °C, which

were recrystallized from isopropanol; IR (ATR) 3052, 2874, 2820 cm^{-1}; $[\alpha]_D^{rt} = -138.7$ (*c* 1.5, THF); ^1H NMR ($CDCl_3$): δ 1.90 (m, 7H), 2.17 (m, 1H), 2.50–3.07 (m, 6H), 3.79 (m, 1H), 4.22 (m, 2H), 7.13 (m, 1H), 7.34 (m, 4H), 12.27 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.3, 23.8, 32.3, 52.9, 54.4, 60.5, 63.7, 122.7, 139.5, 179.9; DEI-MS *m/z* 290 for $C_{16}H_{24}N_3S^+$ ($M+H^+$); Anal. Calcd for $C_{16}H_{23}N_3S$: C, 66.39; H, 8.01; N, 14.52; S, 11.08. Found: C, 66.39; H, 8.41; N, 14.56, S, 10.89.

4.2.2. (*S*)-2-(Morpholin-4-ylmethyl)-*N*-phenylpyrrolidine-1-carbothioamide 8b. Mp 191–195 °C (recrystallization from isopropanol); IR (ATR) 3251–2868 cm^{-1}; $[\alpha]_D^{rt} = -200.0$ (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.84 (m, 2H), 1.94 (m, 2H), 2.45 (m, 4H), 2.84 (m, 2H), 3.59–3.76 (m, 5H), 4.21 (m, 2H), 7.22 (m, 1H), 7.37 (m, 4H), 11.45 (s, NH); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.6, 52.9, 54.0, 58.8, 66.1, 66.6, 125.6, 126.3, 128.9, 140.6, 182.2; DEI-MS *m/z* 306 $C_{16}H_{24}N_3OS^+$ ($M+H^+$); Anal. Calcd for $C_{16}H_{23}N_3OS$: C, 62.92; H, 7,59; N, 13.76; S, 10.50. Found: C, 62.76; H, 7.59; N, 13.65; S, 10.50.

4.2.3. *N*-Phenyl-(*S*)-2-(piperidin-1-ylmethyl)pyrrolidine-1-carbothioamide 8c. Mp 140 °C (recrystallization from isopropanol); IR (ATR) 3179–2920 cm^{-1}; $[\alpha]_D^{rt} = -141.3$ (*c* 1.5, THF); ^1H NMR ($CDCl_3$): δ 1.54–1.97 (m, 9H), 2.18 (m, 1H), 2.40 (m, 3H), 2.74 (m, 3H), 3.82 (m, 1H), 4.24 (m, 2H), 7.19 (m, 1H), 7.35 (m, 4H), 11.98 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.4, 23.7, 25.7, 32.5, 53.0, 55.1, 59.3, 66.3, 125.1, 126.2, 128.5, 140.8, 182.0; DEI-MS *m/z* 304 $C_{17}H_{26}N_3S^+$ ($M+H^+$); Anal. Calcd for $C_{17}H_{25}N_3S$: C, 67.29; H, 8.30; N, 13.85; S, 10.56. Found: C, 67.08; H, 8.54; N, 14.07; S, 10.41.

4.2.4. *N*-(4-Methoxyphenyl)-(*S*)-2-(pyrrolidin-1-yl-methyl)pyrrolidine-1-carbothioamide 8d. Mp 147 °C (recrystallized from EtOH); $[\alpha]_D^{rt} = -138.7$ (*c* 1.5, THF); IR (ATR) 3470, 2972–2830 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74–1.87 (m, 7H), 2.16 (m, 1H), 2.50 (m, 1H), 2.58 (m, 2H), 2.78 (m, 2H), 3.02 (m, 1H), 3.76 (s, 4H), 4.13–4.19 (m, 2H), 6.84 (d, $J = 8.2$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 12,14 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.4, 23.7, 32.3, 53.0, 54.2, 55.4, 60.4, 63.4, 113.7, 126.2, 134.1, 156.6, 181.8; DEI-MS *m/z* 319 $C_{17}H_{25}N_3OS^+$ (M^+); HRMS *m/z* 320.1797 $(M+H)^+$, $C_{17}H_{26}N_3OS$ requires 320.1796.

4.2.5. *N*-(4-Methoxyphenyl)-(*S*)-2-(morpholin-4-ylmethyl)pyrrolidine-1-carbothioamide 8e. Mp 153 °C (recrystallized from EtOH); $[\alpha]_D^{rt} = -158.8$ (*c* 1.7, THF); IR (ATR) 3255, 3047–2818 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.73–1.88 (m, 3H), 2.18 (m, 1H), 2.51 (m, 3H), 2.74 (m, 3H), 3.59 (m, 4H), 3.72 (m, 1H), 3.78 (s, 3H), 4.15 (m, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H), 11.36 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.4, 32.5, 53.0, 53.8, 55.3, 58.8, 65.9, 66.6, 113.9, 127.8, 133.2, 157.3, 182.3; DEI-MS *m/z* 335 $C_{17}H_{25}N_3O_2S^+$ (M^+); Anal. Calcd for $C_{17}H_{25}N_3O_2S$: C, 60.87; H, 7.51; N, 12.53; S 9.56. Found: C, 60.78; H, 7.85; N, 12.49; S, 9.39.

4.2.6. *N*-(4-Methoxyphenyl)-(*S*)-2-(piperidin-1-ylmethyl)pyrrolidine-1-carbothioamide 8f. Mp 80 °C (recrystallized from EtOH); $[\alpha]_D^{rt} = -136.3$ (*c* 1.6, THF); IR (ATR) 3211, 3023–2804; ^1H NMR ($CDCl_3$): δ 1.39 (m, 2H), 1.48 (m, 4H), 1.71 (m, 1H), 1.87 (m, 2H), 2.21 (m, 1H), 2.38 (m, 3H), 2.73 (m, 3H), 3.74 (m, 1H), 3.80 (s, 3H), 4.16 (m, 1H), 4.19 (m, 1H), 6.88 (d, $J = 8.9$ Hz, 2H), 7.20 (d, $J = 8.9$ Hz, 2H), 11.90 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.4, 23.7, 25.7, 32.5, 53.0, 54.8, 55.3, 59.3, 66.2, 113.8, 127.9, 133.7, 157.2, 182.4; DEI-MS *m/z* 333 $C_{18}H_{27}N_3OS^+$ (M^+); Anal. Calcd for $C_{18}H_{27}N_3OS$: C, 64.83; H, 8.16; N, 12.60; S 9.61. Found: C, 64.65; H, 8.53; N, 12.54; S, 9.64.

4.2.7. *N*-Isopropyl-(*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carbothioamide 8g. Mp 82 °C; IR (ATR) 3208, 2960–2820 cm^{-1}; $[\alpha]_D^{rt} = -131.1$ (*c* 1.8, THF); ^1H NMR ($CDCl_3$) 1.23 (t, $J = 6.5$ Hz, 6H), 1.69–1.80 (m, 7H), 2.11 (m, 1H), 2.33 (m, 1H), 2.47 (m, 2H), 2.69 (m, 2H), 2.86 (m, 1H), 3.66 (m, 1H) 3.82 (m, 1H), 4.11 (m, 1H), 4.56 (sept, $J = 6.6$ Hz, 1H), 9.73 (s, NH); ^{13}C NMR ($CDCl_3$): δ 22.1, 23.2, 23.4, 23.7, 32.8, 46.5, 52.7, 54.2, 60.0, 63.8, 180,1; DEI-MS *m/z* 255 $C_{13}H_{25}N_3S^+$ (M^+); HRMS *m/z* 256.1845 $(M+H)^+$, $C_{13}H_{26}N_3S$ requires 256.1847.

4.2.8. *N*-Isopropyl-(*S*)-2-(morpholin-4-ylmethyl)pyrrolidine-1-carbothioamide 8h. Mp 128–130 °C (recrystallization from EtOH); IR (ATR) 3213, 2962–2820 cm^{-1}; $[\alpha]_D^{rt} = -91.0$ (*c* 2.0, THF); ^1H NMR ($CDCl_3$): δ 1.20 (t, $J = 6.9$ Hz, 6H), 1.63–1.76 (m, 3H), 2.02 (m, 1H), 2.25 (m, 1H), 2.39 (m, 2 H), 2.58–2.61 (m, 3H), 3.55–3.68 (m, 5H), 3.84 (m, 1H), 3.97 (m, 1H), 4.60 (sept, $J = 6.6$ Hz, 1H), 8.44 (s, NH); ^{13}C NMR ($CDCl_3$): δ 23.0, 23.4, 23.5, 32.8, 46.9, 52.3, 54.2, 58.5, 66.5, 179.7; DEI-MS *m/z* 272 $C_{13}H_{26}N_3OS^+$ ($M+H^+$); Anal. Calcd for $C_{13}H_{25}N_3OS$: C, 57.53; H, 9.28; N, 15.48; S, 11.81. Found: C, 57.41; H, 9.68; N, 15.57; S, 11.59.

4.2.9. *N*-Isopropyl-(*S*)-2-(piperidin-1-ylmethyl)pyrrolidine-1-carbothioamide 8i. Mp 76–78 °C; IR (ATR) 3211, 2926–2800; $[\alpha]_D^{rt} = -110.0$ (*c* 1.0, THF); ^1H NMR ($CDCl_3$): δ 1.20 (d, $J = 6.9$ Hz, 3H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.46–1.80 (m, 9H), 2.07 (m, 1H), 2.20–2.30 (m, 3H), 2.57 (m, 3H), 3.67 (m, 1H), 3.80 (m, 1H), 4.09 (m, 1H), 4.62 (sept, $J = 6.8$ Hz, 1H), 9.12 (s, NH); ^{13}C NMR ($CDCl_3$): δ 22.7, 23.4 (2×), 23.8, 25.4, 33.2, 46.9, 52.5, 55.1, 59.0, 66.8, 179.6; DEI-MS *m/z* 269 $C_{14}H_{27}N_3S^+$ (M^+); HRMS *m/z* 270.2007 $(M+H)^+$, $C_{14}H_{28}N_3S$ requires 270.2004.

4.3. General procedure for preparation of chiral ureas 9a–c starting from 1–3

4.3.1. *N*-Phenyl-(*S*)-2-(pyrrolidin-1-ylmethyl)-pyrrolidine-1-carboxamide 9a. Compared to **8a**, 1.6 M solution of *n*-butyllithium in *n*-hexane (4.1 mL, 6.5 mmol) was dropped to a −30 °C cooled solution of **1** (1 g, 6.5 mmol) in anhydrous THF (20 mL) with stirring under an inert

atmosphere. The yellow mixture was warmed at room temperature and stirred for 1 h. Afterwards, **6** (0.77 g, 6.5 mmol) was added and the solution was stirred for 2 h. The solvent was evaporated (10 mL). The residue poured into ice water and the obtaining white precipitate was filtered off. After washing with *n*-heptane, **9a** was afforded as a white solid in analytical purity, mp 85 °C; IR (ATR) 3230–3054, 2967–2877, 1670 cm^{-1}; $[\alpha]_D^{rt} = -53.3$ (*c* 1.8, EtOH); ^1H NMR ($CDCl_3$) 1.67 (m, 1H), 1.84 (m, 2H), 1.93 (m, 4H), 2.14(m, 1H), 2.47 (m, 1H), 2.52 (m, 2H), 2.83 (m, 2H), 2.94 (m, 1H), 2.99 (m, 1H), 3.40 (m, 1H), 3.87 (m, 1H), 6.96 (m, 1H), 7.24 (m, 2H), 7.41 (m, 2H), 10.97 (s, NH); ^{13}C NMR ($CDCl_3$): 23.6, 23.9, 32.5, 47.2, 54.7, 57.1, 64.5, 118.9, 121.5, 128.9, 141.1, 156,7; DEI-MS *m*/*z* 273 for $C_{16}H_{23}N_3O^+$ (M^+); Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.31; H, 8.49; N, 15.37. Found: C, 70.51; H, 8.37; N, 15.44.

4.3.2. (*S*)-2-(Morpholin-4-ylmethyl)-*N*-phenylpyrrolidine-1-carboxamide 9b. Mp 165 °C; IR (ATR) 3230–2850, 1661 cm^{-1}; $[\alpha]_D^{rt} = -62.1$ (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.70 (m, 1H), 1.87 (m, 2H), 2.14 (m, 1H), 2.45 (m, 1H), 2.60–2.80 (m, 5H), 3.48 (m, 1H), 3.80 (m, 5H), 4.02 (m, 1H), 7.05 (m, 1H), 7.30 (m, 2H), 7.47 (m, 2H), 9,95 (s, NH); ^{13}C NMR ($CDCl_3$): 23.6, 32.2, 47.1, 54.6, 56.0, 66.7, 120.0, 122.3, 128.8, 140.1, 156.5; DEI-MS *m*/*z* 290 $C_{16}H_{24}N_3O_2^+$ ($M+H^+$); Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.45; H, 7.96; N, 14.49.

4.3.3. *N*-Phenyl-(*S*)-2-(piperidin-1-ylmethyl)pyrrolidine-1-carboxamide 9c. Mp 178 °C; IR (ATR) 3230–2877, 1661 cm^{-1}; $[\alpha]_D^{rt} = -60.8$ (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.54 (m, 2H), 1.67 (m, 5H), 1.82 (m, 2H), 2.11 (m, 1H), 2.30–2.70 (m, 6H), 3.37 (m, 1H), 3.83 (m, 1H), 3.97 (m, 1H), 6.99 (m, 1H), 7.31 (m, 2H), 7.51 (m, 2H), 10.49 (s, NH); ^{13}C NMR ($CDCl_3$): 23.6, 23.9, 25.6, 32.3, 47.1, 55.6, 56.4, 67.1, 120.1, 121.9, 128.6, 140.6, 156.9; DEI-MS *m*/*z* 287 $C_{17}H_{25}N_3O^+$ (M^+); Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 70.89; H, 8.72; N, 14.76.

4.4. General procedure for preparation of chiral guanidines 10a–c

4.4.1. *N,N′*-Isopropyl-(*S*)-2-(pyrrolidin-1-ylmethyl)-pyrrolidine-1-carboximidamide 10a. According to the reported method above, a solution of *n*-butyllithium in *n*-hexane (4.1 mL, 6.5 mmol) was dropped to a solution of **1** (1 g, 6.5 mmol) in dry THF (20 mL) at −30 °C. After stirring for 1 h at room temperature, **7** (0.82 g, 6.5 mmol) was added and the mixture was allowed to react for 2–4 h at ambient temperature. After concentration under reduced pressure, the obtained viscous residue was dissolved in water. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The organic phases were dried ($MgSO_4$) and the solvent was removed under vacuum to afford guanidine **10a** as a dark yellow oil. After workup the crude material was purified by bulb to bulb distillation to afford 1.31 g of **10a** as a colourless oil. Bp 142 °C at 7.2×10^{-2} Torr; IR (ATR) 3226, 2962–2784, 1623 cm^{-1}; $[\alpha]_D^{rt} = -3.0$ (*c* 9.6, THF); ^1H NMR (THF-d_8, −40 °C) 0.94 (d, $J = 6.1$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 6H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.70 (m, 2H), 1.63–1.74 (m, 9H), 1.98 (m, 1H), 2.23 (m, 1H), 2.41–2.53 (m, 5H), 3.21 (m, 2H), 3.39 (sept, 1H), 3.42 (sept, 1H), 4.03 (d, $J = 10.4$ Hz, NH), 4.22 (m, 1H); ^{13}C NMR (THF-d_8, −40 °C) 23.1, 24.2, 24.7, 25.6, 25.7, 26.5, 31.5, 46.6, 47.7, 50.8, 55.4, 56.2, 61.6, 153.1; DEI-MS *m*/*z* 281 for $C_{16}H_{33}N_4$ ($M+H^+$); Anal. Calcd for $C_{16}H_{32}N_4$: C, 68.52; H, 11.50; N, 19.98. Found: C, 68.30; H, 11.74; N, 19.81.

4.4.2. *N,N′*-Diisopropyl-(*S*)-2-(morpholin-4-ylmethyl)-pyrrolidine-1-carboximidamide 10b. Bp 160 °C at 7.2×10^{-2} Torr; IR (ATR) 3368, 2961–2805, 1623 cm^{-1}; $[\alpha]_D^{rt} = -11.1$ (*c* 7.4, THF); ^1H NMR (THF-d_8, −40 °C): δ 0.92 (d, $J = 5.9$ Hz, 3H), 1.03 (t; $J = 6.7$ Hz, 6H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.56–1.74 (m, 5H), 1.90–2.10 (m, 4H), 2.50 (m, 1H), 2.62 (m, 1H), 2.90 (m, 1H), 3.23 (m, 2H), 3.37 (m, 1H), 3.44 (m, 1H), 3.63 (m, 4H), 3.98 (s, NH), 4.27 (m, 1H); ^{13}C NMR (THF-d_8, −40 °C): δ 22.7, 24.4, 25.2, 25.5, 26.1, 31.4, 46.3, 47.7, 50.6, 54.1, 54.6, 55.4, 64.4, 67.3, 152.8; DEI-MS *m*/*z* 297 for $C_{16}H_{33}N_4O^+$ ($M+H^+$); Anal. Calcd for $C_{16}H_{32}N_4O$: C, 64.82; H, 10.88; N, 18.90. Found: C, 64.55; H, 10.93; N, 19.14.

4.4.3. *N,N′*-Diisopropyl-(*S*)-2-(piperidin-1-ylmethyl)-pyrrolidine-1-carboximidamide 10c. Bp 150 °C at 7.2×10^{-2} Torr; IR (ATR) 3396, 2962–2748, 1623 cm^{-1}; $[\alpha]_D^{rt} = -16.6$ (*c* 8.2, THF); ^1H NMR (THF-d_8, −40 °C): δ 0.91 (d, $J = 6.0$ Hz, 3H), 1.03 (t, $J = 7.1$ Hz, 6H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.40–1.75 (m, 9H), 1.93 (m, 1H), 2.00 (m, 1H), 2.42 (m, 1H), 2.77 (m, 2H), 3.12 (m, 2H), 3.21 (m, 2H), 3.37 (sept, 1H), 3.58 (sept, 1H), 4.00 (d, $J = 9.7$ Hz, NH), 4.22 (m, 1H); ^{13}C NMR (THF-d_8, −40 °C): δ 22.8, 24.4, 25.2, 25.3, 26.3, 27.8, 31.5, 46.3, 47.3, 50.4, 54.2, 55.2, 57.3, 64.7, 152.7; DEI-MS *m*/*z* 295 for $C_{17}H_{35}N_4^+$ ($M+H^+$); Anal. Calcd for $C_{17}H_{34}N_4$: C, 69.34; H, 11.64; N, 19.03. Found: C, 69.00; H, 11.64; N, 19.24.

4.5. Crystal structure determination

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects.[27,28] The structures were solved by direct methods (SHELXS[29]) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97[30]). For the amine groups of **8a**, **8d**, **8h** and **9c** the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All other only hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.[30] The absolute configuration of **8a**, **8d** and **8h** could be determined by the X-ray analysis. XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

4.5.1. Crystal data for 8a.[31] $C_{16}H_{23}N_3S$, $M_r = 289.43\,g\,mol^{-1}$, colourless prism, size $0.03\times0.03\times0.02\,mm^3$, monoclinic, space group $P2_1$, $a = 9.4089(2)$, $b = 11.3880(4)$, $c = 14.6592(6)$ Å, $\beta = 96.983(1)°$, $V = 1559.06(9)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd} = 1.233\,g\,cm^{-3}$, μ (Mo-K$_\alpha$) = $2.02\,cm^{-1}$, $F(000) = 624$, 6397 reflections in $h(-11/12)$, $k(-14/14)$, $l(-18/18)$, measured in the range $1.40° \leqslant \Theta \leqslant 27.45°$, completeness $\Theta_{max} = 98.5\%$, 6397 independent reflections, 4467 reflections with $F_o > 4\sigma(F_o)$, 369 parameters, 1 restraints, $R1_{obs} = 0.056$, $wR^2_{obs} = 0.113$, $R1_{all} = 0.097$, $wR^2_{all} = 0.130$, GOOF = 1.048, Flack-parameter −0.09(8), largest difference peak and hole: $0.213/-0.285\,e\,Å^{-3}$.

4.5.2. Crystal data for 8d.[31] $C_{17}H_{25}N_3OS$, $M_r = 319.46\,g\,mol^{-1}$, colourless prism, size $0.03\times0.03\times0.02\,mm^3$, monoclinic, space group $P2_1$, $a = 5.6592(2)$, $b = 18.6338(7)$, $c = 8.0998(3)$Å, $\beta = 98.914(1)°$, $V = 843.83(5)$ Å^3, $T = -90$ °C, $Z = 2$, $\rho_{calcd} = 1.257\,g\,cm^{-3}$, μ (Mo-K$_\alpha$) = $1.98\,cm^{-1}$, $F(000) = 344$, 3324 reflections in $h(-7/7)$, $k(-24/20)$, $l(-10/10)$, measured in the range $3.36° \leqslant \Theta \leqslant 27.47°$, completeness $\Theta_{max} = 99.1\%$, 3324 independent reflections, 2643 reflections with $F_o > 4\sigma(F_o)$, 203 parameters, 1 restraints, $R1_{obs} = 0.048$, $wR^2_{obs} = 0.105$, $R1_{all} = 0.070$, $wR^2_{all} = 0.114$, GOOF = 1.041, Flack-parameter −0.07(9), largest difference peak and hole: $0.779/-0.238\,e\,Å^{-3}$.

4.5.3. Crystal data for 8h.[31] $C_{13}H_{25}N_3OS$, $M_r = 271.42\,g\,mol^{-1}$, colourless prism, size $0.04\times0.04\times0.02\,mm^3$, orthorhombic, space group $P2_12_12_1$, $a = 9.5064(3)$, $b = 9.8967(3)$, $c = 15.5969(5)$ Å, $V = 1467.39(8)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd} = 1.229\,g\,cm^{-3}$, μ (Mo-K$_\alpha$) = $2.15\,cm^{-1}$, $F(000) = 592$, 3301 reflections in $h(-12/12)$, $k(12/12)$, $l(-20/20)$, measured in the range $2.61° \leqslant \Theta \leqslant 27.45°$, completeness $\Theta_{max} = 99.4\%$, 3301 independent reflections, 2717 reflections with $F_o > 4\sigma(F_o)$, 167 parameters, 0 restraints, $R1_{obs} = 0.039$, $wR^2_{obs} = 0.081$, $R1_{all} = 0.056$, $wR^2_{all} = 0.088$, GOOF = 1.013, Flack-parameter −0.14(8), largest difference peak and hole: $0.171/-0.197\,e\,Å^{-3}$.

4.5.4. Crystal data for 9c.[31] $C_{17}H_{25}N_3O$, $M_r = 287.40\,g\,mol^{-1}$, colourless prism, size $0.03\times0.03\times0.03\,mm^3$, orthorhombic, space group $P2_12_12_1$, $a = 6.2521(2)$, $b = 12.8953(4)$, $c = 19.0078(6)$ Å, $V = 1532.46(8)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd} = 1.246\,g\,cm^{-3}$, μ (Mo-K$_\alpha$) = $0.79\,cm^{-1}$, $F(000) = 624$, 3463 reflections in $h(-8/8)$, $k(-16/16)$, $l(-24/24)$, measured in the range $2.66° \leqslant \Theta \leqslant 27.47°$, completeness $\Theta_{max} = 99.7\%$, 3463 independent reflections, 2714 reflections with $F_o > 4\sigma(F_o)$, 194 parameters, 0 restraints, $R1_{obs} = 0.045$, $wR^2_{obs} = 0.092$, $R1_{all} = 0.071$, $wR^2_{all} = 0.102$, GOOF = 0.995, Flack-parameter 1.6(15), largest difference peak and hole: $0.160/-0.193\,e\,Å^{-3}$.

4.5.5. Crystal data for 10a·(HCl)$_2$.[31] $[C_{16}H_{34}N_4]^{2+}$ $2Cl^- * C_2H_3N$, $M_r = 394.43\,g\,mol^{-1}$, colourless prism, size $0.03\times0.03\times0.02\,mm^3$, monoclinic, space group $P2_1$, $a = 6.1469(3)$, $b = 16.3789(9)$, $c = 11.0017(4)$ Å, $\beta = 99.701(3)°$, $V = 1091.81(9)$ Å^3, $T = -90$ °C, $Z = 2$, $\rho_{calcd} = 1.200\,g\,cm^{-3}$, μ (Mo-K$_\alpha$) = $3.08\,cm^{-1}$, $F(000) = 428$, 6552 reflections in $h(-6/7)$, $k(-21/20)$, $l(-14/13)$, measured in the range $2.25° \leqslant \Theta \leqslant 27.48°$, completeness $\Theta_{max} = 99.7\%$, 4620 independent reflections, $R_{int} = 0.032$, 3853 reflections with $F_o > 4\sigma(F_o)$, 239 parameters, 1 restraints, $R1_{obs} = 0.043$, $wR^2_{obs} = 0.088$, $R1_{all} = 0.060$, $wR^2_{all} = 0.095$, GOOF = 1.006, Flack-parameter −0.06(5), largest difference peak and hole: $0.234/-0.237\,e\,Å^{-3}$.

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